# The relationship between habitual physical activity status and executive function in individuals with Alzheimer's disease: a longitudinal, cross-lagged panel analysis

Article (Accepted Version)

# The relationship between habitual physical activity status and executive function in individuals with Alzheimer's disease: A longitudinal, cross-lagged panel analysis.

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## Abstract

**Objectives:** To determine whether habitual physical activity status specifically influences executive function change in Alzheimer's Disease (AD) over 1 year.

**Methods**: In this longitudinal cohort study, 45 participants with AD were recruited and provided follow up data approximately 1 year later. Executive function measures (map search task, digit symbol substitution task, controlled oral word association task, verbal fluency task) and habitual physical activity measures (physical activity scale in the elderly (PASE) and handgrip strength) were taken at baseline and follow up. Individual composites were subsequently created. Additional demographic, lifestyle and neuropsychiatric measures were also taken.

**Results:** In a structural equation model ($\chi^2$ (26) = 9.84, p = .998, CFI = 1.00, RMSEA = .00) a significant association was found between habitual physical activity and executive function change (β= .27, p= .04). In a cross-lagged panel analysis a significant path was found between the PASE score and executive change (β=.22, p= .01).

**Discussion:** As higher habitual physical activity levels were associated with reduced executive function change, the promotion of low-intensity habitual physical activities in individuals with a diagnosis of AD may be warranted. Further research is needed, however, to explore the impact of habitual physical activity on the trajectory of change across cognitive domains, and how this relates to the progression of the underlying pathology associated with this disease.


KEY TERMS: Physical activity, cognition, Alzheimer's disease, exercise, executive function

## Introduction

Alzheimer's disease (AD) is a neurodegenerative condition that results in the progressive decline of cognitive performance. A meta-analysis of the literature has reported that individuals with AD decline an average of 3.3 Mini-mental state examination (MMSE) points annually (Han, Cole, Bellavance, McCusker, & Primeau, 2000). However, it is important to note that there is significant variability between individuals (Hui et al., 2003), and that in AD there are stages in which global cognitive decline plateaus (Bozoki et al., 2009; Haxby et al., 1992; Piccini et al., 1995). Variations in cognitive trajectory can be attributed to a multitude of factors including age, severity and years of education (e.g. Scarmeas, Albert, Manly, & Stern, 2006; Teri, Mccurry, Edland, Kukull, & Larson, 1995), and also to the temporal sequencing of cognitive change as it associates with the anatomically localised time course of the underlying pathology (Fox et al., 1996; Fox et al., 1999; Scahill et al., 2002).

Executive function is the cognitive process involved in the planning, initiation and regulation of behaviour (Lezak, 2004). Executive function has consistently been found to be impaired early in the disease course (Binetti et al., 1996; Collette et al., 1999; Lafleche & Albert, 1995). Even prior to the clinical diagnosis of AD, executive deficits can differentiate between those that go onto develop the disease and those that do not (Albert et al., 2001; Sgaramella et al., 2001). However, the majority of literature is cross-sectional in design and therefore little is known about the trajectory of executive function change within an AD population. Understanding more about the rate of executive function decline in AD is a prerequisite for identifying factors that might alter the trajectory, allowing a more direct approach to maintaining functionality, where executive function plays a vital role (Martyr & Clare, 2012).

One potential moderator of the executive function trajectory in AD is physical activity. A systematic review of published randomised control trials (RCTs) on this topic in an AD population found that physical activity interventions have a positive effect on cognitive function in AD (Farina, Rusted, & Tabet, 2013). Whilst this highlights the potential of physical activity to positively affect cognition, how it specifically affects the trajectory of executive decline is unclear, since the majority of those RCTs report global cognitive function rather than domain specific outcomes. In addition, physical activity interventions in AD have been relatively short lived and can span anywhere between 4 weeks (Rolland et al., 2000) and 24 weeks (Hernandez et al., 2010; Venturelli et al., 2011; Yu et al., 2013). This length of intervention may not be sufficient to elicit a sustained shift in the trajectory of executive function decline in AD.

A particular area of interest is the impact of habitual physical activity. Habitual physical activity has previously been defined as the physical activity conducted by individuals in everyday life, and reflects both an individual's ability and their motivation (Farina, Tabet & Rusted, 2014). As such, habitual physical activity encompasses leisure activities (e.g. walking, group sports) but also can include activities that are conducted in the home (e.g. gardening, cleaning) and at work. Evidence for positive effects of habitual physical activity on cognition in an AD population is mixed. Burns et al. (2008) used an extensive battery of cognitive measures but found in the AD sample (mean MMSE= 26.2) only two of the tasks (Trails B and logical memory) were associated with cardiorespiratory fitness (a proxy measure of aerobic habitual physical activity). After controlling for participants' age the association was no longer significant. Research from the present authors previously reported an association between habitual physical activity and executive task performance in an AD population (Farina et al., 2014). Notably, as this research was conducted at a single time

point, conclusions about the effects on trajectory or even the direction of the effect were limited.

Only a few studies have explored the effects of habitual physical activity on cognitive change in AD longitudinally. Vidoni and colleagues found that that baseline cardiorespiratory fitness was positively associated with dementia severity change in AD patients (CDR = 0.5 and 1) followed up over 2 years (Vidoni, Honea, Billinger, Swerdlow, & Burns, 2012). Winchester and colleagues explored the effects of habitual physical activity on cognitive change over a 1-year period in 104 AD patients (MMSE>18; Winchester et al., 2013). Based upon walking habits alone, participants were split into an active (engaged in more than 2 hours of walking per week) and a sedentary group (did not engage in any walking). Those in the active group at baseline showed a significant improvement in MMSE over 1 year, whilst the MMSE of the sedentary group significantly declined. Both studies implicate habitual physical activity as a factor in the rate of global cognitive change in AD. To date, no studies have reported the effects of habitual physical activity specifically on the trajectory of executive function decline.

Limited literature exists in an AD population regarding the best type of physical activity to elicit an effect, with heterogeneity of intervention types in the reported RCTs (Farina et al., 2013), and studies that have explored the association between habitual physical activity and cognition in AD have used a variety of proxy measures of habitual physical activity. For example, Burns et al. (2008) and Vidoni et al. (2012) measured cardiorespiratory fitness, reflecting aerobic physical activity. Winchester et al. (2013) measured a variety of physical activities, but only investigated the relationship between walking and cognition. This is problematic as it assumes that only aerobic activities are able to positively affect cognition. In

a meta-analysis of the healthy older adult RCT literature it was reported that aerobic exercise interventions have a greater effect on cognitive speed and visual attention compared to any other intervention type (Angevaren et al., 2008). A more recent review reported that aerobic activity and strength training have a positive effect on cognition in healthy older adults, whilst stretching and flexibility activities do not (Clifford et al., 2009). It has also been suggested that participating in novel and multiple physical activities is more important (Bielak, 2010). Clearly, the positive effects of specific types of physical activity on cognition are still under debate.

The present study focus is on disentangling the longitudinal impact of habitual physical activity on executive function in an AD population, over a twelve month period.

Based upon previous research suggesting that habitual physical activity can combat global cognitive decline in AD (Vidoni et al., 2012; Winchester et al., 2013) it is hypothesised that habitual physical activity will be significantly associated with trajectory of change. We will consider the direction of this relationship as inferred from a cross-lagged panel analysis, controlling for potential confounding effects of other physiological indices of physical status. Determining whether habitual physical activity can affect the trajectory of executive function decline will inform clinicians' recommendations to patients and their carers regarding the benefits of an active lifestyle.

## Methods

### *Participants*

Ethical approval was obtained from the National Research Ethics Service Committee London – Camberwell St Giles.

The AD patients were aged 65-90 and were all fluent in English. Eligible participants had previously been clinically assessed using the International Statistical Classification of Diseases, 10th revision (ICD-10; World Health Organization, 1992), and received a diagnosis of probable dementia of Alzheimer's type or atypical AD with a mild to moderate severity (MMSE>12). AD patients were excluded if they had a major depressive disorder (Cornell Scale of Depression in Dementia >10). AD patients were recruited through Sussex Partnership NHS Trust. AD patients all had a personal consultee (relative or friend), and were either clinically or self-referred.

***Materials***

A MMSE score was derived from the Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) to provide a standardised measure of global cognitive status. The Cornell Scale of Depression in Dementia (CSDD; Alexopoulos, Abrams, Young, & Shamoian, 1988) was used to screen for the presence of major depression. The Neuropsychiatric Inventory (NPI; Cummings et al., 1994), a proxy-rated questionnaire on dementia-related behavioural symptoms, was used to assess the presence of psychiatric and behavioural disturbances. The National Adult Reading Test (NART; Nelson, 1982) was used to estimate premorbid IQ.

*Executive measures*

A series of executive function measures were selected:

Trail Making Task (TMT; Army Individual Test Battery, 1944): participants were required (Trails A) to connect numbers distributed on the page in ascending order, and then (Trails B) to connect, alternately, sequential numerical and alphabetical stimuli. Participants were instructed to complete the tasks as quickly and accurately as possible. Both parts of the TMT

were scored in time to completion (seconds). Subtracting Trails A from Trails B we derived a measure of executive control, corrected for motor and visual scan speed.

Controlled Oral Word Association Test (COWAT; Spreen & Strauss, 1998): participants verbally listed words beginning with the letters F, A and S with a fixed time limit of 60 seconds for each letter. Following standard instructions, participants were instructed that they should not list proper nouns or supply the same words but with a different ending. The COWAT was scored as the total number of allowable words generated across the three letters.

Verbal fluency subscale of the ACE-R (Mioshi et al., 2006): this was composed of two tasks. In the first task participants verbally listed words beginning with the letter P in a fixed time limit of 60 seconds. In the second task participants had to list as many animals as possible within 60 seconds.

Map Search Task (Robertson et al., 1994): this is a component of the Test of Everyday Attention battery. Participants were required to locate target symbols (e.g. restaurant) on a city map, and have 2 minutes to circle as many target symbols as possible. The Map Search Task is scored on the total number of target symbols accurately identified during the time limit. Primarily a visual search task, the Map Search Task requires higher order decision making and executive planning to optimise search strategy and differentiate relevant from non-relevant symbols under timed conditions.

Digit Symbol Substitution Test (DSST) (Wecshler, 1981): The task is composed of two phases. In the first phase, participants were required to copy out a symbol sequence for 30 seconds. In the second phase, participants were given a code table displaying the correspondence between digits (from 1 to 9) and symbols. Participants were required to fill in blank squares with the symbol paired to the digit displayed above the square. The mean time

per item was calculated for each phase. Subtracting the DSST copy score from phase two score provided the decision time (DT) required per symbol substitution decision (Glosser et al., 1977; Storandt, 1976).

Card sort task (Rusted, Sawyer, Jones, Trawley, & Marchant, 2009): the task involves sorting a regular deck of playing cards (52 cards) generated on the computer screen. On each trial, the back of the card is presented for 1000 ms, reversing to show the face of the card for 750 ms. Participants are instructed to sort the cards into 'SPADES' and 'HEARTS' by pressing the designated keys on the keyboard using their right hand. Participants are told to ignore the 'CLUBS' or 'DIAMONDS'. The program automatically advances onto the next card trial. Mean reaction time taken per sort trial provide a measure of decision making speed (DMS).

*Lifestyle measures*

A series of lifestyle measures were administered by questionnaires to the carer of the participant.

Physical activity was measured using the Physical Activity Scale for the Elderly (PASE; Washburn, Smith, Jette, & Janney, 1993). The PASE comprises 12 items addressing the leisure, household and work over the past week. The PASE has previously been validated against physiological measures of physical activity including accelerometer (Washburn & Ficker, 1999), mini-logger (Harada et al., 2001), peak oxygen uptake and balance score (Washburn et al., 1999). The questionnaire is validated for completion by carers of dementia patients (Burns et al., 2008, 2010; Honea et al., 2009).

Cognitive activities were measured using the Florida Cognitive Activities Scale (FCAS; Schinka et al., 2005). The scale consists of 25-items using a 5-point Likert response format based on activity frequency. The FCAS has with a reasonably high level of internal

consistency (α= .65) for an elderly Caucasian sample. The FCAS has also been validated for use with people with AD (Schinka et al., 2010).

Social network was assessed using the Lubben Social Network Scale – 6 (LSNS-6**;** Lubben, 1988). The LSNS-6 is a 6 item scale, 3 items concerning family and 3 concerning friendships. The scale is scored out of 30, with a greater score representing a larger social network. It is been shown to have a high internal consistency (α= .78; Lubben & Gironda, 2003).

Adherence to a Mediterranean diet was assessed using the EPIC Food Frequency Questionnaire (FFQ; Bingham et al., 2007). A value of 0 or 1 was assigned for each of 9 indicated categories with the use of the sex-specific median as the cut-off; thus adherence to a Mediterranean diet score ranged from 0 to 9, with a greater score representing a greater adherence to a Mediterranean diet (Cade et al., 2011; Trichopoulou et al., 2003).

*Physiological Measures*

Several physiological measures were taken to index physical status.

Handgrip strength was measured using a dynamometer (T.K.K.5401 Grip D, Accuracy: ±2.0 kgf). Using their dominant hand participants were instructed to squeeze the dynamometer as hard as they could. Participants repeated this procedure three times with the best score being recorded. In older adults handgrip strength has been found to be positively associated with other muscle groups (Rantanen et al., 1994) as well was measures of physical activity (Bruce et al., 2002; Rantanen et al., 1994). In dementia populations, increased physical activity has also been associated with increased handgrip strength (e.g. Francese et al., 1997). Handgrip strength can therefore be considered an acceptable proxy of physical status and physical ability in our AD participants.

Mid-upper arm circumference (MUAC) was measured by placing a plastic tape measure gently but firmly around the relaxed arm, midway between the tip of the acromion (shoulder) and the olecranon process (elbow). Waist circumference was measured at the point of the iliac crest, whilst the calf circumference was measured around the largest point of the calf. Measurements of height and weight were used to calculated BMI (weight [kg] over height squared [$m^2$]). MUAC, calf circumference, waist circumference and BMI have all previously been associated with nutritional status in an older adult population (Nykänen et al., 2013; Ruiz-López et al., 2003).

***Procedure***

Participants were consented and tested individually. The battery of neuropsychology tests, incorporating the tasks reported in this paper and other non-executive cognitive measures not reported here, lasted approximately 2-3 hours. The AD population were encouraged to take a break when needed. The pen and paper cognitive tasks conducted in the first part of the battery, and the computerised tasks in the second half. Participants subsequently completed the same measures approximately 1 year later.

***Data analysis***

Comparisons made between groups, or between different time points, were analysed using a Student's t-test and paired t-test respectively. As not all data were parametric, a common resampling technique (bootstrapping) was employed. Bootstrap analysis is frequently used to address the problem of possible skewness in the distribution of a variable. This is achieved by resampling the study data to create a large number of bootstrap samples. The present study used 1000 bootstrap samples that were bias-corrected and accelerated. Effect sizes (Cohen's d) were also calculated, correcting for the correlation between time points.

The measures DT, Trails B-A, Map search task, card sort DMS, COWAT and ACE-R verbal fluency subscale were entered into a principal component analysis (PCA) using Oblimin rotation (delta=0). Based on the interpretation of a skree plot, all measures moderately loaded (>.40) onto a single component and accounted for 48.14% of the variance. On this basis, a composite "executive function" was created and a z score composite was calculated using the average of the standardised variables. In the creation of the composite, listwise deletion was employed. In order to ensure that sufficient power was maintained, cognitive tasks were only included in the final composite if they were completed by more than 75% of the sample population. Both the card sort DMS (27%) and Trails B-A (47%) had a high rate of non-completion in $T_2$. Participants unable to complete these tasks had a significantly lower MMSE at follow-up compared to those that were able to complete the Trails B-A (p=.001) and card sort DMS (p=.05). As a consequence the final "executive function" composite was made up of the DT, Map Search Task, COWAT and ACE-R verbal fluency subscale. Notably, however, a significant positive correlation was found between Trails B-A, a conventional measure of executive function, and the composite measure (r= .61, p<.001). A second PCA was conducted entering measures of physical status (PASE, handgrip strength, MUAC, BMI, CC and WC). Two components were identified which, based on the interpretation of the skree plot, accounted for 62.87% of the variance. MUAC, CC, WC and BMI all moderately loaded onto a single component (>.40). As all these measures have previously been associated with nutritional status in older adults (Nykänen, Lönnroos, Kautiainen, Sulkava, & Hartikainen, 2013; Ruiz-López et al., 2003) the composite "nutritional status" was created. The PASE score and handgrip strength moderately loaded (>.40) onto the second component of the PCA. Both handgrip strength and PASE are accepted as proxies of habitual physical activity (e.g. Bruce et al., 2002; Washburn et al.,

1993), and a significant moderate correlation was found between handgrip strength and PASE score (r=.43, p=.003); so the composite "habitual physical activity status" was created.

A structural equation model (SEM) was created between baseline habitual physical activity status and executive function change score (executive function $T_2$ – executive function $T_1$). Analysis included the following covariates: age, premorbid IQ, NPI, FCAS, LSNS-6, nutritional status and MeDi. A path was created between all covariates and executive function change. In the model covariates were allowed to correlate with each other and habitual physical activity status based upon significant bivariate correlations. Paths were eliminated initially based upon the lowest weighted non-significant path ($p>.05$); the elimination of any path was only kept if at least a single model fix index (see below) showed an improvement. If any model fit indices decreased, the eliminated path was reintroduced.

A standard two-wave cross-lagged panel design was used to test the existence of a causal relationship between the composite factor of physical activity (PASE and Handgrip strength) and executive function across the baseline and follow-up time points. Subsequently, for comparative purpose, a second two-wave cross-lagged panel analysis was conducted, this time investigating the relationship between physical activity and global cognitive function (MMSE).

Model fit was assessed using the following statistics: the $\chi^2$ statistic, the Comparative Fit Index (CFI), and the Root Mean Square Error of Approximation (RMSEA). A non-significant $\chi^2$ indicates a good model fit. For the RMSEA, values less than 0.07 indicate a good fit (Steiger, 2007), whilst a CFI value $\geq 0.95$ is indicative of good fit (Hu & Bentler, 1999).

## Results

### *Attrition*

Of the initial 100 participants recruited, 85 participants provided useable data at baseline testing phase, following drop-outs and exclusions. A subset of seventy-one participants were available to contact the following year, twenty six were lost to follow-up. Participants that were lost to follow-up had a significantly lower baseline MMSE ($p = .02$) compared to those that were followed-up. Age, premorbid IQ, years since diagnosis, gender, NPI and PASE score did not differ significantly in those that were lost to follow-up ($p > .05$; See Table 1).

(Table 1 about here)

### *Descriptive data and preliminary analyses*

At baseline participants had a mean age of 81.5 (SD= 5.9), mean premorbid IQ of 115.4 (SD= 8.1), mean MMSE of 24.5 (SD = 2.8), and on average had been diagnosed for 1.1 years (SD= 1.7); 49% were male (Table 1). The means and standard deviations of cognitive and lifestyle outcomes at each time point are presented in Table 2. Total PASE score, handgrip strength, FCAS and LSNS-6 all declined significantly between $T_1$ and $T_2$. Further inspection of PASE scores revealed that only household related physical activity declined significantly ($p < .01$), leisure and work related activities were unchanged ($p > .05$). Measures of global cognitive function (MMSE and ACE-R) both declined significantly between $T_1$ and $T_2$ ($p \leq .01$). Comparing executive composite (DT, Map search task, COWAT and ACE-R fluency subscale) at both time points, a significant decline was apparent between $T_1$ and $T_2$ ($d = .52$, $p = .01$).

(Table 2 about here)

***Structural Equation Modelling***

A structural equation model examined whether the moderate change in executive function observed over the 12 month follow-up could be linked to differences in habitual physical activity. An initial model was created: $\chi^2(23) = 9.50$, $p = .994$, CFI = 1.00, RMSEA = .00. Three non-significant paths were identified (NPI T1 → Executive function change; NPI T1 →age; nutritional status T1 → Executive function change), in which deletion improved the model fit index ($\chi^2$). A final model was therefore created without these paths: $\chi^2 (26) = 9.84$, $p = .998$, CFI = 1.00, RMSEA = .00 (Figure 1). A significance path was found between habitual physical activity status and executive function (HPA status T1 → Executive Function Change = .27, $p = .04$). Age (Age → Executive function change = .29, $p = .01$), premorbid IQ (premorbid IQ → Executive function change = .35, $p < .01$) and cognitive activities (FCAS → Executive function change = .34, $p = .02$) all significantly predicted executive function change. Adherence to a MeDi (MeDi → Executive function change = -.23, $p = .06$) also trended toward significantly predicting executive function change. The only covariate that did not significantly predict executive function change was social network size (LSNS-6 → Executive function change = .13, $p = .29$) although removing this path did not improve the model fit.

(Figure 1 about here).

***Cross-lagged panel analysis – Executive Function***

In the cross-lagged panel analysis, the habitual physical activity composite was split into PASE and handgrip strength to explore which aspect of habitual physical activity affects cognitive change. Between the two time points, paths between habitual physical activity (PASE T1 → PASE T2 = .75, $p < .001$), handgrip strength (Handgrip T1 → Handgrip T2 =

.92, p < .001) and executive function (Executive function T1→ Executive function T2 = .85, p < .001) were significant.

Cross-lagged paths from PASE ($T_1$) to executive function at follow-up were significant (PASE T1 → Executive function T2 = .22, p= .01) but baseline executive function did not significantly predict habitual physical activity at follow-up (Executive function T1 → PASE T2 = -.04, p =.70). Baseline handgrip strength did not predict executive function at follow-up (Handgrip T1 → Executive Function T2 = -.12, p = .14) but executive function at baseline did predict handgrip strength at follow-up (Executive Function T1 → Handgrip T2 = .13, p= .01). The data significantly fit the model ($\chi^2$ (5) = 3.02, p = .70, CFI = 1.00, RMSEA = .00 (Figure 2)).

(Figure 2 about here)

***Cross-lagged panel analysis – Global cognitive function***

Between the two time points, paths between habitual physical activity (PASE T1 → PASE T2 = .72, p < .001), handgrip strength (Handgrip T1 → Handgrip T2 = .94, p < .001) and global cognition (MMSE T1→ MMSE T2 = .71, p< .001) were significant. However, cross-lagged paths between PASE and MMSE, and between handgrip strength and MMSE were non-significant (p>.05). For full model see Figure 3. The data significantly fit the model ($\chi^2$ (5) = 5.22, p = .39, CFI = 1.00, RMSEA = .03.

(Figure 3 about here)

## Discussion

The objective of the study was to determine whether levels of habitual physical activity significantly predict executive performance change over one year in an AD population. Following the creation of an SEM, and supported by a cross-lagged panel analysis, the data support the hypothesis that in the cohort of AD patients tested here, levels of habitual physical activity significantly predicted executive function change over a period of 12 months.

The executive function composite declined significantly between $T_1$ and $T_2$, showing a moderate effect size (*d*= .52). Thus in practical terms, executive decline in this sample seems to be prominent over the duration of the study. Somewhat surprisingly, the mean performance of many of the individual executive function tasks (DT, Trails B-A, Card Sort DMS, Map Search and COWAT) displayed no significant decline between $T_1$ and $T_2$ in our AD volunteers. The ACE-R verbal fluency subscale was the only individual contributor to the executive function composite to decline significantly between $T_1$ and $T_2$, displaying a moderate effect size (*d*=.59). All measures included in the model loaded on a single factor in the preliminary principle components analysis, that we termed "executive function". They do not, however, all measure the exact same process. For example, the ACE-R verbal fluency task is a composite of letter fluency and category naming, and the latter is associated with temporal-lobe activation (Cerhan et al., 2001). The early degeneration of this cortical area in AD is responsible for the common finding that letter naming is often more intact compared to category naming (Crossley et al., 1997; Monsch et al., 1994; Salmon et al., 1999). Our current finding is not inconsistent with a temporal ordering of cognitive deficits in AD, whereby episodic and semantic memory deficits occur earlier in the course of the disease compared to executive function (Carter et al., 2012). In fact, the composite executive function

change noted here may load more heavily on semantic fluency than on executive function change. Further research is needed to precisely explore the trajectories of decline of 'executive function' tasks across the temporal staging of the disease. In particular, longitudinal studies which explore the relationship between lifestyle factors and domain specific cognitive progression at different stages of the disease would be useful.

Despite this caveat, the SEM employed here demonstrated a significant path between habitual physical activity status and executive function change over one year in an AD population, supporting our initial hypothesis that habitual physical activity status can moderate the trajectory of executive decline. Importantly, this relationship remained after controlling for confounding variables such as age, premorbid IQ, cognitive activities, social network, nutritional status and adherence to a MeDi. As stated in a recent review by Smith and colleagues, it is important that other lifestyle factors such as diet and cognition are accounted for, since they tend to cluster together (Smith, Potter, McLaren, & Blumenthal, 2013). Health behaviours in particular are often clustered, and a change in one is often associated with a change in another (Pate et al., 1996). For example, individuals that voluntarily increase their physical fitness were more likely to change their dietary habits than those that do not (Blair, Goodyear, Wynne, & Saunders, 1984; Wilcox, King, Castro, & Bortz, 2000). In addition, there is substantive evidence that they too may affect the onset of dementia (e.g. Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Sattler, Toro, Schönknecht, & Schröder, 2012; Wilson et al., 2002).

A cross-lagged panel analysis was conducted to further interrogate the data. The cross-lagged analysis revealed a stronger path between PASE (T1) and Executive function (T2) compared to the path between Executive function (T1) and PASE (T2). This provides some evidence

for a directional relationship between habitual physical activity as measured by the PASE and executive function change. As the present sample had both participants that improved executive function as well as declined it is possible that there is threshold level of habitual physical activity that the individual has to achieve to impact executive function decline. Further work should explore this with a larger sample of volunteers and over a longer time frame. Interestingly the association between PASE (T1) and change was present after controlling for handgrip strength (T1). This finding allows for us to better determine what type of physical activity affects executive function change in AD. Controlling for handgrip strength highlights that the activities measured in the PASE do not have to be of a type or intensity to elicit muscle development. This finding needs further research, but offers preliminary support for the notion that a variety of physical activities is more beneficial that a specific type or intensity (Bielak, 2010). Notably, the ability of PASE to predict cognitive decline only existed for the executive function composite. When a similar cross-lagged panel analysis was conducted against MMSE, a measure of global cognitive function measure, neither PASE score nor handgrip strength predicted MMSE change. This supports previous evidence from healthy older adults (Colcombe & Kramer, 2003) and an MCI population (Gates et al., 2013) that physical activity selectively affects executive function, though the evidence is far from conclusive (e.g. Angevaren et al., 2008; Smith et al., 2010). In the present study, the selective impact of the verbal fluency measure argues, again, for a cautious confirmation of the relationship with executive function.

Habitual physical activity, cognitive activities and social network were also all found to significantly decline between $T_1$ and $T_2$ in AD. The total PASE score showed the largest effect size ($d$ = 0.75), indicating that out of the lifestyle factors measured habitual physical activity is the most impacted by disease progression. Little research has been conducted into

longitudinal change in leisure activities in AD. In healthy older adults, there is evidence that individuals may reduce leisure time physical activity in older age (Dallosso et al., 1988; Yusuf et al., 1996). However, different constraints are likely to underlie participation by cognitively impaired populations. In the present study also, when analysing the subcomponents of the PASE score, only the household related activities declined significantly between $T_1$ and $T_2$ (d = 0.77). Therefore, if habitual physical activity can affect executive trajectory, as reported here, further research should explore the potential barriers for AD patients to participate in these activities, and how best to overcome them.

A key limitation in the present study is the high attrition rates between baseline and 1 year follow-up. Although this is not uncommon in an AD population, it is important to be cautious in the interpretation of the results, particularly considering that those that were lost to follow-up had significantly lower MMSE scores. Primarily, the attrition could affect external validity, with the population less likely to be representative of a more moderate severity AD population. Also, the high attrition resulted in a smaller sample size, which potentially limits the interpretation of the statistical analysis of the study. SEM can successfully be performed in small sample sizes (e.g. n=50, Iacobucci, 2010), although due to increased risk of Type II errors it is important that non-significant associations are not disregarded until the study can be replicated with a larger sample size.

It is also important to highlight the difficulty of accurately measuring habitual physical activity status in a dementia population. Self-report measures of physical activity are commonly used with older adults, but for people with dementia recall accuracy is an issue. The only measure of physical activity developed and validated for a dementia population with a mild severity (Hauer et al., 2011) was published after the onset of our study.

Consequently, the PASE (an established measure of physical activity in older adults) was adapted so that carers, who are likely to have an intimate knowledge of the participant's day-to-day activities, could complete the measure. Nevertheless, such proxy completed measures are susceptible to reporter bias or even gaps where informant is unaware of the patients' habits. In the present study, creating a composite of habitual physical activity status of PASE score and the objective measure of handgrip strength was intended to address this problem, by combining a objective measure with the carer report.

This study was not intended as an exploration of the mechanisms mediating habitual physical activity and executive function but future research should address this aspect. One potential mediator is the ability of physical activity to improve vascular health and cerebrovascular perfusion (e.g. Ainslie et al., 2008; Rogers, Meyer, & Mortel, 1990). Poor vascular health is a common pathological marker for AD (Kalaria & Ballard, 1999; Kalaria, 2002) and is an established risk factor for the disease (O'Brien & Markus, 2014). It is likely that a measure of vascular health would have explained additional variance in our model. Confirming vascular health as a mediating factor would have practical implications, with regard to the type, duration and intensity of physical activity required to have an effect.

In summary, the present study has extended previous literature by investigating the effects of differences in habitual physical activity on longitudinal change in executive function in an AD population over a 12 month period. In support of the initial hypothesis, there was evidence that habitual physical activity status significantly predicted change on a composite measure of executive function. In addition, a cross-lagged panel analysis inferred a stronger, causal relationship by establishing a significant path between baseline PASE score and executive function change, but not between baseline executive function and PASE change.

Looking at individual elements of the composite, however, revealed that the relationship was driven by changes in verbal fluency, and further work, over a longer time frame, is needed to map the trajectory of change in the other contributing executive function tasks. Nevertheless, the result suggest that low-intensity habitual physical activity could be promoted by clinicians to people with dementia, for its potential benefits with minimal cost implications and adverse effects. Ultimately, identifying factors that maintain executive function in AD could assist individuals to remain functionally independent for longer. There are still many questions that need answering, however, including the mechanism by which habitual physical activity effects executive function trajectory in AD, and the time frame over which such benefits are likely to emerge. Based on the present study the promotion of non-specific habitual physical activity is indicated as beneficial for this clinical population.

## Conflicts of Interest

None


## Funding

This work was supported by the Economic Social and Research Council (grant number ES/102803X/1); and Sussex Partnership NHS Foundation Trust.

## Acknowledgements

Thank you to Jeremy Young who participated in the collection of the data from the control sample. Thank you to Dr Wim Calame and Dr Rod Bond, for their assistance and advice on the statistical analysis. The authors also like to thank Dr. Kathryn Hart, a nutritionist, for her consultation and processing of FFQs and the EPIC-Norfolk Study team for the use of the EPICFFQ. EPIC-Norfolk is supported by program grants from the Medical Research Council UK (G9502233, G0300128) and Cancer Research UK (C865/A2883).

A special thanks to all the participants that agreed to take part in the study.


***Word Count:*** *5482 words*

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**Table 1.** The means (and SD) of key baseline characteristics of those that were lost and not lost to follow-up. Significance level reported (Based on 1000 bootstrap sample, 95% BCa).

| | Followed-up (n=45) | Lost to Follow-up (n=26) | P |
|---|---|---|---|
| Age | 81.5 (*6.0*) | 81.2 (*5.2*) | .84 |
| Gender | 22 Male/23 Female | 9 Male/ 17 Female | .24 |
| Premorbid IQ | 115.4 (*8.1*) | 110.7 (*10.2*) | .06 |
| MMSE | 24.5 (*2.8*) | 22.2 (*4.4*) | .02 |
| Years since Diagnosis | 1.1 (*1.7*) | .9 (*.9*) | .51 |
| PASE | 91.63 (*55.01*) | 63.26 (63.*50*) | .06 |
| NPI | 5.0 (*7.8*) | 8.4 (*10.6*) | .12 |

MMSE= Mini-mental state examination, NPI = Neuropsychiatric Inventory, PASE= Physical Activity Scale for the Elderly

Table 2. The means (and standard deviations) of lifestyle and cognitive measures. A paired t-test was conducted between time points (based on 1000 bootstrapped sample, 95% BCa) with Effect Sizes (ES; Cohen's d) calculated.

| | $T_1$ | $T_2$ | ES | p |
|---|---|---|---|---|
| Measures of habitual physical activity | | | | |
| PASE total | 93.03 (*55.40*) | 64.75 (*47.41*) | 0.75 | <.01 |
| Leisure subscale | 20.85 (*28.76*) | 17.75 (*25.67*) | 0.21 | .17 |
| Household subscale | 71.77 (*40.57*) | 46.72 (*35.97*) | 0.77 | <.01 |
| Work Subscale | .42 (*2.03*) | .28 (*1.83*) | 0.15 | .12 |
| Handgrip Strength (kg) | 26.00 (*9.32*) | 24.68 (*9.59*) | 0.39 | <.001 |
| Other Lifestyle Measures | | | | |
| Cognitive Activities | 34.5 (*11.3*) | 27.7 (*10.1*) | 0.66 | <.01 |
| LSNS-6 | 16.8 (*4.9*) | 15.4 (*4.7*) | 0.36 | .03 |
| Global Cognition | | | | |
| MMSE | 24.5 (*2.8*) | 23.0 (*4.6*) | 0.55 | <.01 |
| ACE-R Total | 70.7 (*9.7*) | 67.3 (*13.1*) | 0.46 | .01 |
| Executive measures | | | | |
| Trail B –A (seconds) | 90.62 (*50.43*) | 86.86 (*44.15*) | 0.01 | .63 |
| Map Search (total correct) | 32.0 (*16.1*) | 36.5 (*18.4*) | 0.28 | .12 |
| DT (time per item)(seconds) | 3.57 (*4.28*) | 3.82 (*4.54*) | 0.05 | .81 |
| Card sort DMS (RT correct)(seconds) | 827.97 (*201.82*) | 870.16 (*215.54*) | 0.25 | .18 |
| COWAT (total correct) | 27.3 (*11.1*) | 26.7 (*11.7*) | 0.07 | .65 |
| ACE-R fluency (total correct) | 7.4 (*2.6*) | 6.1 (*3.1*) | 0.59 | <.01 |

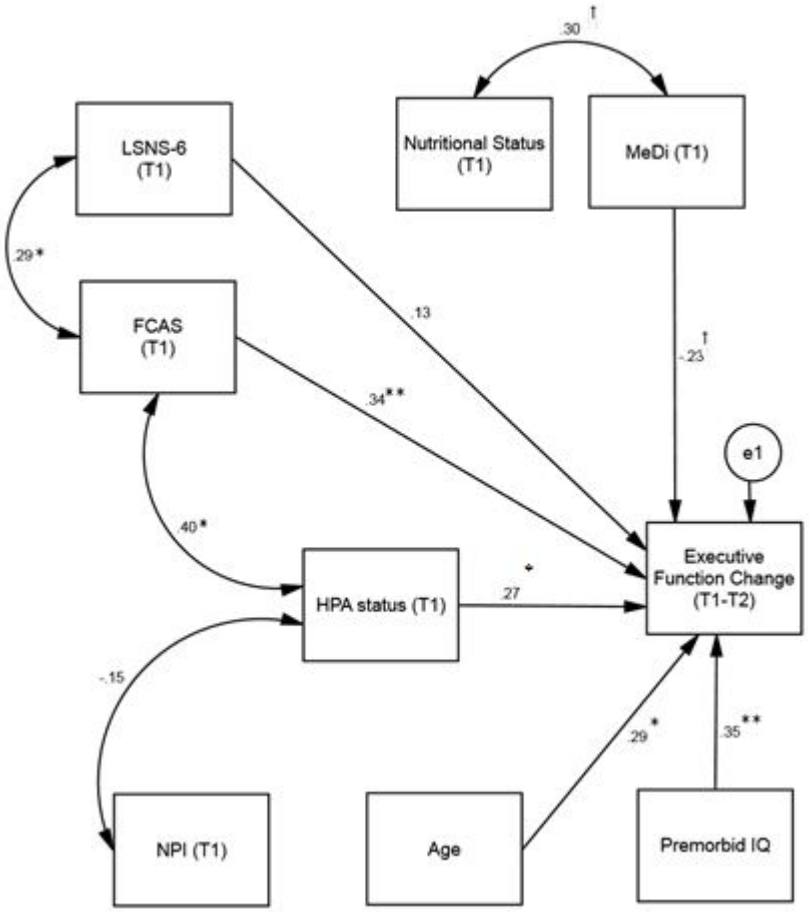


**Figure 1.** The effects of Habitual Physical Activity (HPA) status on executive function change between time points in an AD population, the final model. Age, premorbid IQ, Florida Cognitive Activity Scale (FCAS), Lubben Social Network Scale-6 (LSNS-6), nutritional status, and Adherence to a Mediterranean Diet (MeDi) were all controlled for. Standardised regression weights showed. † $p \leq .06$, * $p < .05$, ** $p < .01$, *** $p < .001$.

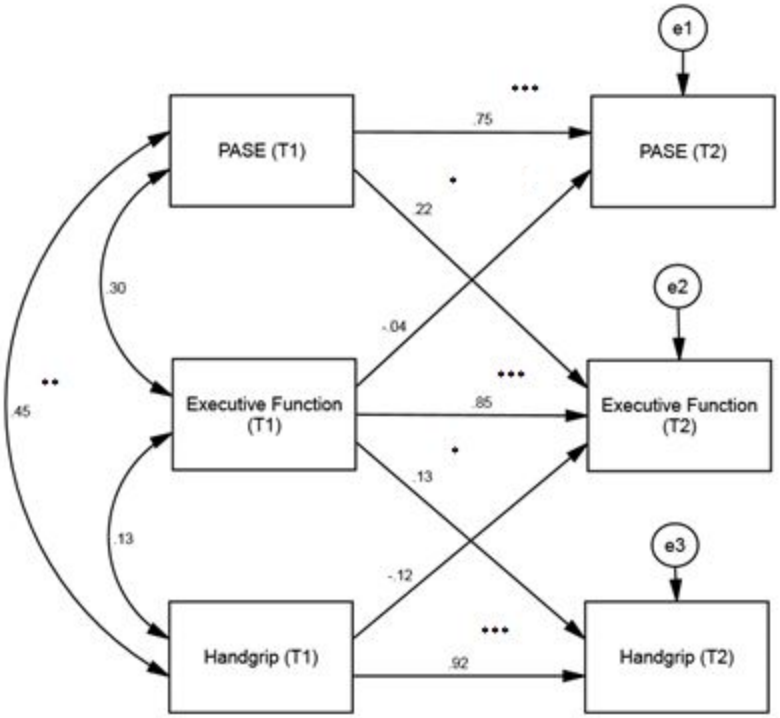


**Figure 2.** A cross-lagged panel analysis between PASE, handgrip strength and executive function. * p< .05, ** p < .01, *** p< .001.

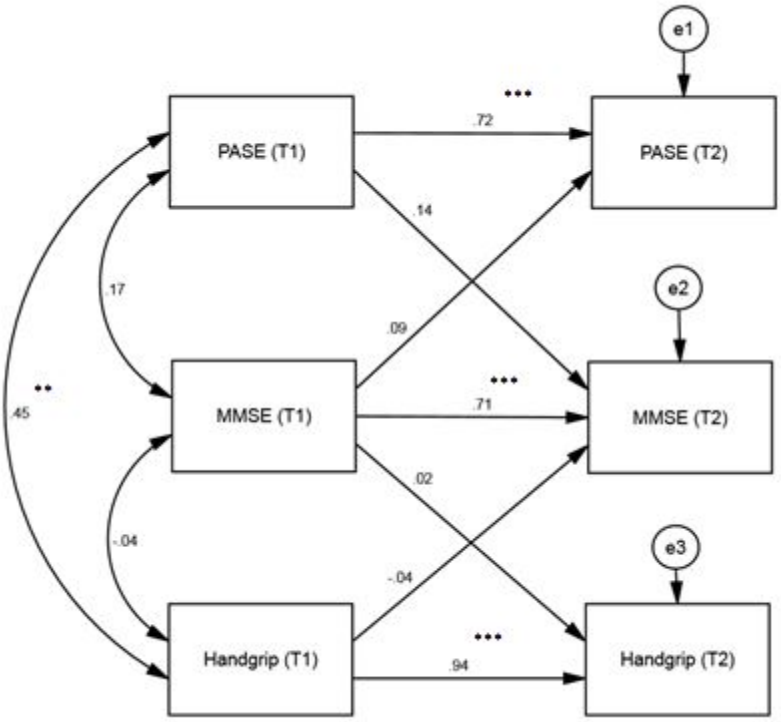


**Figure 3.** A cross-lagged panel analysis between PASE, handgrip strength and MMSE. * p< .05, ** p < .01,